ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

ISSN 1425-9524
© Ann Transplant, 2016; 21: 336-345
DOI: 10.12659/AOT.896672

Received: 2015.11.13
Accepted: 2016.01.05
Published: 2016.05.31

Reduction of Cold Ischemia Time and Anastomosis Time Correlates with Lower Delayed Graft Function Rates Following Transplantation of Marginal Kidneys

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Source of support: Departmental sources

Background: In kidney transplantation, the association of cold ischemia time (CIT), anastomosis time (AT), and delayed graft function (DGF) is particularly detrimental in grafts from marginal donors; however, actual cut-off criteria are still debated.

Material/Methods: Data from patients >65 years (n=193) and patients <65 years (n=1054) transplanted between 2000 and 2010 were retrospectively analyzed regarding the age-dependent impact of ischemia times and DGF.

Results: Overall death censored graft survival was inferior for ECD/DCD organs. Graft survival was significantly impaired by DGF in younger and older recipients. The multivariate analysis revealed an age-dependent profile of risk factors for DGF. In younger patients, multiple risk factors were identified while in patients >65 years, only CIT and AT were correlated with DGF. Marginal grafts with a CIT<769 min had a comparable outcome to any SCD organ; extended CIT >770 min worsened ECD/DCD survival significantly. Similarly, AT longer than 26 min was associated with a significantly impaired survival of ECD/DCD grafts. In a Cox regression analysis with penalized splines, this increased risk of graft loss was not linear: CIT beyond 800 min and AT beyond 20 min were cut-off values associated with worse outcomes in marginal organs.

Conclusions: Thus, risk factors for DGF are age-dependent; keeping ischemia times below these thresholds offers outcome of ECD/DCD organs comparable to SCD organs.

MeSH Keywords: Cold Ischemia • Frail Elderly • Kidney Transplantation • Warm Ischemia

Full-text PDF: http://www.annalsoftransplantation.com/abstract/index/idArt/896672

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Strategies to optimize the utilization of "marginal" expanded criteria donor (ECD), such as the implementation of the Eurotransplant Senior Program (ESP), have led to a better utilization and outcome of ECD organs [1]. However, further means are required to expand the donor pool and utilize "very marginal" grafts for transplantation. Reduction of delayed graft function (DGF) is particularly crucial in highly marginal grafts [1–5]. Since elderly grafts lack a potential for repair and recovery after sustained ischemic injury [6–8], keeping CIT as short as possible has been proven effective in reducing DGF and graft loss4[1,2,9,10]. In addition, warm ischemia time (WIT) causing extensive ATN in grafts from aged donors is known as a major determinant of graft survival in DCD donation [11–13]. However, the correlation of WIT and CIT has not been fully examined in grafts from elderly brain-dead donors (DBD).

Very recently, the adverse impact of vascular anastomosis time – implying warm ischemia during the warming-up process of the kidney – on graft and patient survival has been evaluated at our center [14]. Moreover, AT was shown to correlate with the incidence of DGF and length of hospital stay [15]. While studies demonstrated a general negative effect of prolonged AT, age- and donor-type-dependent influences have not been investigated. This is of particular relevance given the increased susceptibility of ECD organs to ischemic injuries. The correlation of AT and CIT with DGF and subsequent risk of graft loss is key to optimize outcome of older organs. Here, we present one of the largest single-center studies on the age-dependent influence of CIT and anastomosis time on different types of grafts.

Material and Methods

Analysis of data from patient undergoing kidney transplantation from deceased donors

All adult patients (>18 years) undergoing kidney transplantation (KTx) at the University of Innsbruck between 1 January 2000 and 31 December 2010 receiving a deceased donor kidney graft were analyzed retrospectively. The primary endpoint of the study was graft survival according to ischemia times and secondary endpoints were DGF, influence of graft type, and patient survival. The database included patient demographics, indications for transplantation, donor related data, graft function, and acute rejection data as well as graft and patient survival data. Kidneys from donors >65 years of age were mostly allocated through the Eurotransplant Senior Program (ESP), which abandons HLA-matching in order to keep CIT short. All transplantations were AB0 blood group-compatible and had a negative cross-match. Donor data were retrieved from ET donor information sheets. Recipient data were collected from hospital files and wait list documentation.

Following retrieval, grafts were cold stored in HTK solution. Ktx was performed in a standard technique with end-to-side vascular anastomoses to the external iliac vessels and anti-reflux ureterocystostomy. The latter has been performed using the Leadbetter-Politano technique between 2000 and 2006 and using the Lich-Gregoire technique between 2006 and 2010. After 2006, an internal ureteral stent was routinely used and left in place for 10 days.

Immunosuppression in standard patients consisted of a regimen of CNI (cyclosporine (target trough level 180–200 ng/mL), or tacrolimus (target trough level 8–10 ng/mL), mycophenolic acid (1000 mg bid), and methylprednisolone. Patients with high immunological risk (high PRA >50% or retransplantation) received an induction therapy (anti-thymocyte globulin or alemtuzumab) followed by standard triple immunosuppression. Patients receiving kidneys from donors >65 years were treated with an IL-2 receptor antagonist on POD 0 and 4, and mycophenolic acid (1000 mg bid) and methylprednisolone with a delayed CNI onset on POD 4 (tacrolimus starting trough level 8 ng/ml).

After transplantation, graft function (primary function, delayed graft function and primary non-function), clinically suspected and biopsy-proven acute rejection (BxAR), and patient death were monitored. DGF was defined as the need for dialysis within the first week after transplantation, including primary non-function. Rejection episodes were documented according to occurrence (within the first 6 months, 6–12 months, and >12months after transplantation).

All patients were treated according to the local standard protocol. This included postoperative ultrasound control, repeated daily for the first 7 days thereafter. Cold ischemia time (CIT) was defined as the time from cold organ perfusion during the retrieval procedure until start of implantation in the recipient. Anastomosis time (AT) was defined as the time from removing the kidney from the cold preservation solution until reperfusion.

Statistical analysis

Graft survival was calculated from the day of transplantation until the patient died or went back on dialysis. Graft survival was censored for patient death with a functioning graft. Graft and patient survival were calculated using the Kaplan-Meier product-limit estimation approach for different strata.

As a univariate analysis, the chi-square test was used to compare categorical variables and the *t* test or Mann-Whitney U test (if data were not normally distributed) were used to compare continuous variables.

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A logistic regression analysis was used to analyze influences of single patient and operation-related factors on DGF and AR, respectively: age at transplant, biopsy-proven acute rejection, DGF, CIT, AT, Type of donor (SCD *vs.* ECD/DCD), and induction therapy. The risk of graft loss associated with duration of AT and CIT was calculated using a Cox regression analysis with penalized splines.

Descriptive statistics are demonstrated as absolute and relative frequencies for qualitative data and means and standard deviations for quantitative data. P-values <0.05 (two-tailed) were considered statistically significant. Statistical analyses were conducted in R, version 3.1.1, and SPSS, version 22.0 (SPPS Inc, Chicago, IL, USA).

Results

Patient groups

Our study included 1247 adult patients undergoing kidney transplantation at our center between 2000 and 2010. Pediatric patients were excluded. We compared 193 patients aged over 65 years who mostly received grafts from elderly donors through the Eurotransplant Senior Program (ESP) *vs.* 1054 younger patients (<65 years) (Table 1). Despite higher HLA-mismatch rates, acute rejection episodes were comparable. Of note, delayed graft function occurred more frequently in ESP patients, in particular following transplantation of ECD organs.

Impaired survival of marginal grafts in young and old recipients

First, graft, and patient survival were compared between young and old recipients according to donor type (Figure 1). Ten-year patient survival was significantly lower for recipients >65 years and was independent of the type of graft. ECD/DCD and SCD grafts did not affect patient survival in either age group. In contrast, death-censored graft survival strongly depended on the type of graft. Marginal grafts (ECD/DCD) were associated with impaired 10-year graft survival in younger and older patients (p<0.0005).

Determinants of DGF: Cold and warm ischemia time

As shown in Table 1, patients >65 years had a significantly higher DGF rate following DCD or ECD transplantation. Thus, characteristics of young and old recipients with DGF were analyzed (Table 2). In young patients with DGF, a multitude of factors such as donor and recipient age, ischemia times, or highest PRA were significantly different; in contrast, elderly patients with DGF received organs with a longer CIT (about 117 min longer, p<0.003) and a longer anastomosis time (about 5 min longer, p<0.0005) on average than patients with primary function.

Pronounced age-dependent effects of DGF

Given the high rate of DGF in the context of "old for old" transplantation, the consequences of DGF on graft and patient survival were analyzed. In a pairwise comparison, patient survival was not affected by DGF in elderly recipients (Figure 2). However, survival of younger patients was significantly lower if DGF occurred (p<0.0005).

On the other hand, death-censored 10-year graft survival was inferior following DGF in both age groups. Interestingly, comparing grafts with DGF in young and old recipients, grafts in aged patients had a similar outcome, although this group had a significantly different donor organ profile (Table 2, Figure 2). Therefore, recipient-related factors such as an ameliorated immune response may have contributed to an overall stable long-term outcome of ECD/DCD grafts in elderly patients [16,17].

These findings were confirmed in a logistic regression model scrutinizing independent risk factors for DGF (Table 3). In younger recipients, CIT and anastomosis time affected the incidence of DGF. In addition, ECD/DCD grafts with an impaired repair capacity and younger recipient age were identified as further risk factors in this age group. On the contrary, only cold and warm ischemia time affected DGF rates in elderly patients.

Taken together, risk factors for DGF showed a distinct age-related pattern; in elderly recipients only CIT and anastomosis time seemed to be relevant.

Transplantation of ECD grafts with prolonged CIT is associated with worse outcome

Next, the correlation of cold ischemia time and graft survival was analyzed according to donor type. In order to scrutinize effects of different CIT, equally sized groups (tertiles) were assessed according to the duration of CIT <769 min (short), 770–1007 min (medium), and >1008 min (long) (Figure 3).

Duration of CIT did not affect graft survival of younger (SCD) organs, but graft survival was significantly inferior in recipients of ECD/DCD grafts with prolonged CIT compared to ECD grafts with short CIT <769 min (p=0.05). Interestingly, ECD grafts with a short CIT offered an equivalent survival compared to SCD grafts with any duration of CIT.

The risk of ECD graft loss increases beyond 800 min CIT

Because prolonged CIT was strongly associated with a lower survival of marginal grafts, a graft-specific cut-off time was defined by using a Cox regression model with penalized splines (Figure 4). This analysis allowed assessment of a distinct CIT beyond which the risk of graft loss increased. Importantly, the

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Table 1. Patient and donor characteristics.

		Recipient age		Test	P-Value
		<65 yrs (n=1054)	>65 yrs (n=193)		
Recipient age		46.81±11.28	68.16±2.75	T-test	0.0005
Donor age		41.59±15.12	59.49±15.95	T-test	0.0005
BxAR (total)		215 (21.0%)	33 (17.2%)	Chi-Square	0.231
CMV donor	Neg	158 (35.8%)	46 (43.8%)	Chi-Square	0.129
	Pos	283 (64.2%)	59 (56.2%)		
CMV recipient	Neg	363 (38.9%)	56 (30.9%)	Chi-Square	0.042
	Pos	569 (61.1%)	125 (69.1%)		
Anastomosis Time (AT) (min)		30.87±9.58	31.06±9.54	T-test	0.79
Cold Ischemia Time (CIT)(min)		915.1±301.9	850.4±274.5	T-test	0.006
Current PRA		5.17±16.07	5.55±18.45	MWU	0.131
Highest PRA		15.80±26.88	14.07±26.11	MWU	0.387
HLA-A Mismatch	0	327 (31.6%)	55 (28.9%)	Chi-Square	0.029
	1	516 (49.9%)	84 (44.2%)		
	2	191 (18.5%)	51 (26.8%)		
HLA-B Mismatch	0	221 (21.4%)	33 (17.4%)	Chi-Square	0.041
	1	469 (45.4%)	76 (40.0%)		
	2	344 (33.3%)	81 (42.6%)		
HLA-DR Mismatch	0	237 (22.9%)	28 (14.7%)	Chi-Square	0.0005
	1	526 (50.9%)	83 (43.7%)		
	2	271 (26.2%)	79 (41.6%)		
Induction therapy		607 (60.9%)	164 (85%)	Chi-Square	0.0005
Retransplantation	No	831 (80.1%)	170 (88.5%)	Chi-Square	0.006
	Yes	206 (19.9%)	22 (11.5%)		
Donor type	DCD	14 (1.4%)	4 (2.1%)	Chi-Square	0.0005
	ECD	195 (18.8%)	131 (67.9%)		
	SCD	828 (79.8%)	58 (30.1%)		
DGF	No	593 (59.5%)	101 (52.3%)	Chi-Square	0.067
	Yes	404 (40.5%)	92 (47.7%)		
DCD	Primary function	2 (14.3%)	2 (50.0%)	Chi-Square	0.197
	DGF	12 (85.7%)	2 (50.0%)		
ECD primary function	Primary function	72 (38.3%)	66 (50.4%)	Chi-Square	0.039
	DGF	116 (61.7%)	65 (49.6%)		
SCD	Primary function	519 (65.3%)	33 (56.9%)	Chi-Square	0.203
	DGF	276 (34.7%)	25 (43.1%)		

Values are given as means ± standard deviation or absolute and relative frequencies. A p-value <0.05 was considered statistically significant.

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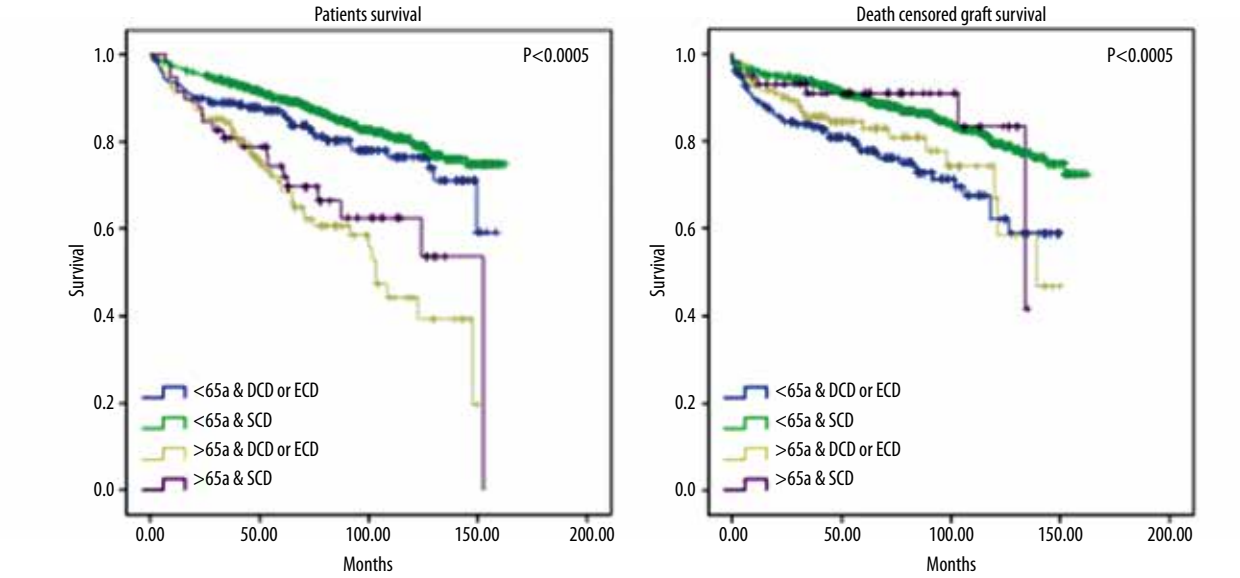

Figure 1. Influence of donor type and recipient age on patient and graft survival. Patient and death censored graft survival following SCD and DCD or ECD kidney transplantation in patients under 65 years and over 65 years of age (blue: <65 years and DCD or ECD graft, green: <65 years and SCD graft, yellow: >65 years and DCD or ECD graft, purple: <65 years and SCD graft). A p-value <0.05 was considered statistically significant. While patient survival of recipients of DCD or ECD grafts was comparable in each age group, graft survival depended significantly on the type of graft as assessed by log-rank test.

Table 2. Characteristics of patients with primary function *vs.* delayed graft function.

	Primary function	DGF	P-value (T-test)
Recipient age <65yrs			
Recipient age	45.64±11.22	48.69±11.13	0.0005
Donor age	39.34±14,81	45.06±14.91	0.0005
Anastomosis time (AT) (min)	29.87±8.88	32.48±10.43	0.0005
Cold ischemia time (CIT) (min)	870.7±294.5	973.7±300.9	0.0005
Current PRA	4.32±15.09	5.98±16.58	0.103
Highest PRA	13.23±24.95	18.59±28.24	0.002
Recipient age >65yrs			
Recipient Age	68.26±2.81	68.05±2.69	0.585
Donor age	58.30±17.26	60.80±14.37	0.279
Anastomosis time (AT) (min)	28.81±8.16	33.59±10.37	0.0005
Cold ischemia time (CIT) (min)	794.7±266.6	912.3±271.3	0.003
Current PRA	4.78±17.60	6.37±19.38	0.555
Highest PRA	14.06±26.19	14.08±26.17	0.994

Patient characteristics according to graft function. Values are given as means ± standard deviation. A p-value <0.05 was considered statistically significant. On average, elderly recipients with DGF had a longer anastomosis time and longer CIT than recipients with primary graft function.

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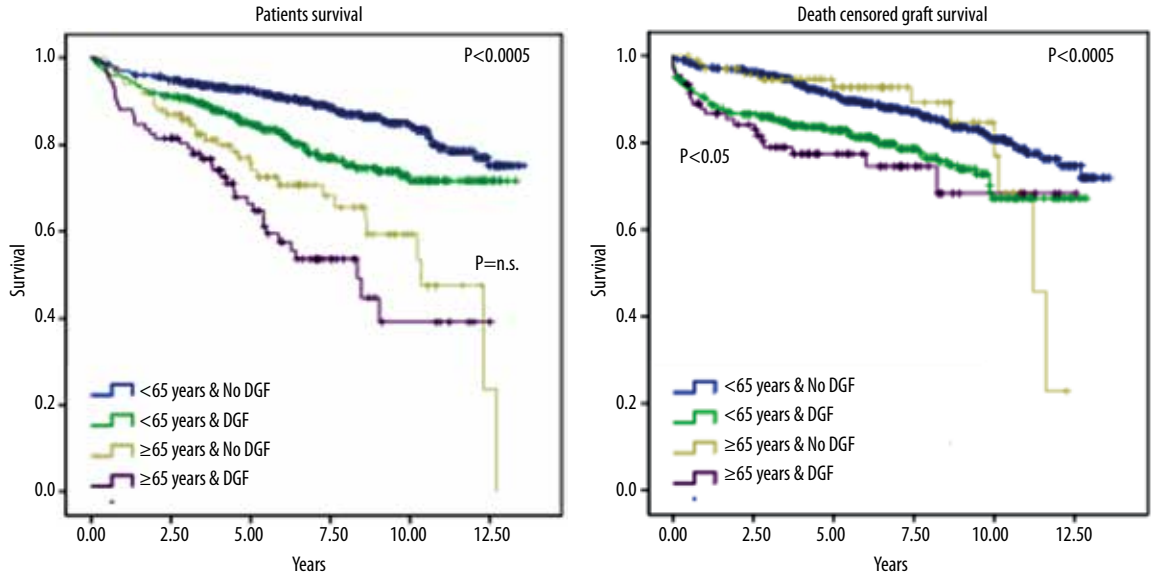

Figure 2. Age-dependent influence of DGF on patient and graft survival. Patient and death-censored graft survival according to the incidence of DGF in patients under 65 years and over 65 years of age (blue: age<65 years, without DGF, green: age<65 years, with DGF, yellow: age>65 years, purple: age>65 years, with DGF). A p-value <0.05 was considered statistically significant. DGF adversely affected 10-year patient survival in younger, but not in older, patients. In contrast, graft survival was significantly inferior in both age groups following DGF. However, comparing survival of grafts with DGF in young and old patients, no differences could be observed.

Table 3. Age-associated pattern of risk factors impacting on DGF.

Equation variable	Odds ratio	95% coinfidence interval	P value
Age <65 years			
Age at Tx	1.02	1.00–1.03	0.006
Donor age	1.01	0.99–1.02	0.099
CIT	1.00	1.00–1.00	0.000
Anastomosis time	1.03	1.01–1.04	0.000
Induction therapy	0.81	0.61–1.07	0.137
DCD Donor	8.64	1.73–37.4	0.008
ECD Donor	2.11	1.37–3.23	0.001
Age >65 years			
Age at Tx	0.96	0.86–1.07	0.423
Donor age	1.01	0.98–1.05	0.481
CIT	1.00	1.00–1.00	0.003
Anastomosis time	1.06	1.02–1.09	0.003
Induction therapy	1.84	0.69–4.83	0.219
DCD Donor	1.35	1.39–13.1	0.799
ECD Donor	1.19	0.36–3.97	0.776

Logistic regression analysis of risk factors for DGF in patients under 65 years and over 65 years of age. A p-value <0.05 was considered statistically significant. In younger recipients, the age at transplant, CIT and AT and ECD or DCD donor status were associated with DGF. In contrast, only CIT and AT affected DGF in elderly recipients.

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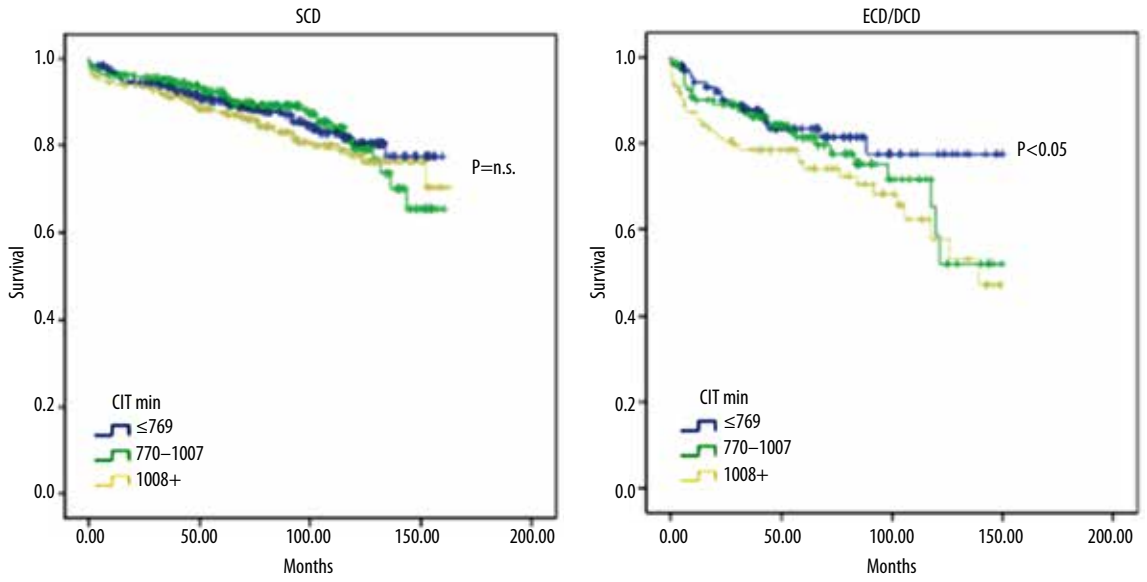

Figure 3. Influence of cold ischemia time (CIT) on graft survival. Death-censored graft survival according to donor type and CIT (blue: CIT ≤769 min, green: CIT 770–1007 min, yellow: CIT ≥1008 min). A p-value <0.05 was considered statistically significant. CIT intervals were defined based on the standard of equally sized groups. Death-censored graft survival was significantly impaired when ECD/DCD kidneys were transplanted with a prolonged CIT, while SCD grafts tolerated longer CIT. Of note, ECD/DCD organs with short CIT yielded a comparable outcome to SCD organs with any CIT.

correlation between CIT and risk of graft loss was not linear; instead, there was a cut-off beyond which the risk increased up to a certain level. As shown in Figure 4, the risk of graft loss for ECD kidneys was stable when CIT was shorter than 800 min but increased dramatically thereafter. For example, at a CIT of 950 min, the hazard ratio compared with the reference value of 800 min is about 1.8 (exp(0.6)=1.8), determining an 80% higher risk of graft loss compared to grafts with a CIT of 800 min. On the contrary, prolongation of CIT beyond 800 min did not significantly affect graft survival of SCD kidneys.

These results demonstrate that reducing CIT below 800 min does not improve ECD/DCD graft outcome, while the risk of graft loss is almost doubled beyond 16 h of CIT.

Same anastomosis time but different outcomes of SCD and ECD grafts.

Anastomosis time (AT) has been the second independent risk factor for DGF in elderly recipients. Therefore, the impact of AT on graft survival was analyzed separately in equally sized groups (tertiles) according to the duration of AT<26 min (short), 27–33 min (medium), and >34 min (long).

SCD grafts did not yield a better survival if AT was short. On the other hand, ECD graft outcome significantly depended on the duration of AT (Figure 5). ECD/DCD grafts with prolonged AT had a worse outcome than grafts with short AT (p<0.05).

Of note, marginal grafts with a short AT <26 min had a comparable graft survival to SCD with any AT.

Anastomosis time of 20 min is crucial for marginal grafts

Next, a Cox regression with penalized splines was used to better define the threshold of warm ischemia for marginal grafts (Figure 6). While the risk of graft loss for SCD organs did not change with prolongation of AT, ECD/DCD kidneys benefited from a short AT. Again, the correlation of AT and risk of graft loss was not linear. The reference value of 20 min AT defined the threshold beyond which the risk of ECD/DCD graft loss increased. For example, the risk of graft loss was significantly higher when AT was 27 min and peaked at 32 min, at which the risk of graft loss was about 2.2-fold higher (exp(0.8)=2.2).

Discussion

Prolonged CIT is a known risk factor for DGF and impaired graft survival, in particular in older donor organs [1,2,9], while DGF is an independent risk factor for lower graft survival and graft loss [3,4]. Bösmüller et al. analyzed outcomes of elderly kidney transplant recipients >70 years, stating that on average

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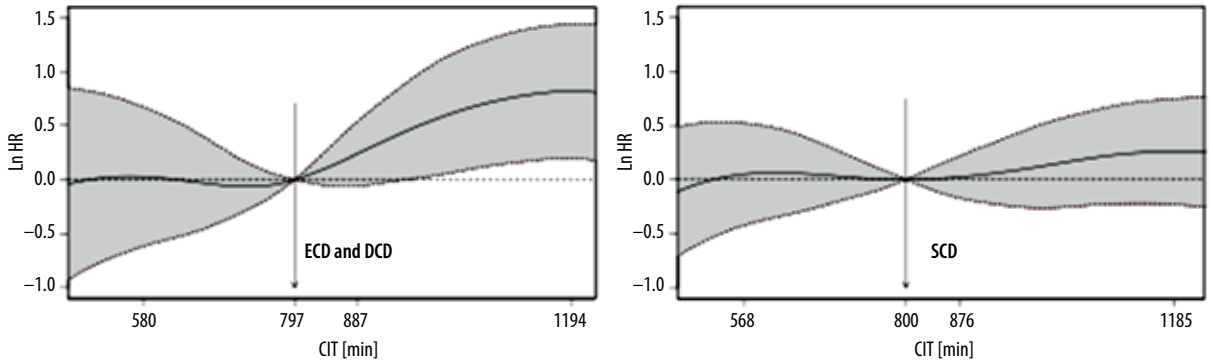

Figure 4. Non-linear, CIT-dependent risk of graft loss. To define a certain CIT representing a graft-specific threshold leading to impaired outcome, a Cox regression with penalized splines was used. While duration of CIT beyond 800 min was associated with an increased risk of graft loss following DCD or ECD transplantation, a CIT longer than 800 min did not significantly affect graft survival of SCD kidneys.

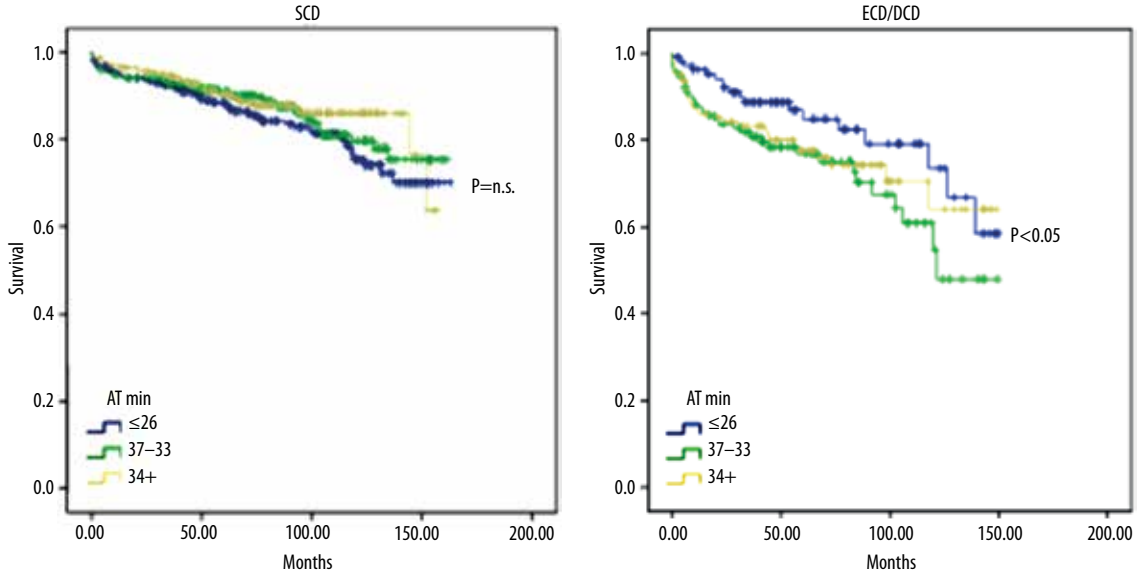

Figure 5. Influence anastomosis time (AT) on graft survival. Death-censored graft survival according to donor type and AT (blue: grafts with AT ≤26min, green: grafts with AT 27–33 min, yellow: grafts with AT ≥34 min). A p-value <0.05 was considered statistically significant. AT intervals were defined based on the standard of equally sized groups. SCD graft survival was unaffected by duration of warm ischemia, while ECD/DCD grafts with prolonged AT had a significantly lower survival compared to grafts with a short AT.

CIT was 3 h longer in patients with DGF [9], but keeping CIT at about 13 h in elderly patients was associated with excellent graft function. These data are in accordance with our findings of an excellent ECD/DCD graft survival when CIT was below 769 min. In our study, DGF was correlated with inferior patient survival in younger but not in elderly patients. These age-dependent findings may be partly explained by different group sizes, which allow for statistical significance in younger patients but not in older patients. In addition, the shorter life expectancy of elderly recipients may have ameliorated the effects of DGF-related patient death.

The Cox regression analysis confirmed a threshold of 800 min (=13.3 h), beyond which the risk of graft loss increased. Likewise, Bahde et al. reported reduced graft survival in ESP patients if CIT exceeded 15 h (=900 min), which was confirmed by our risk analysis based on penalized splines.

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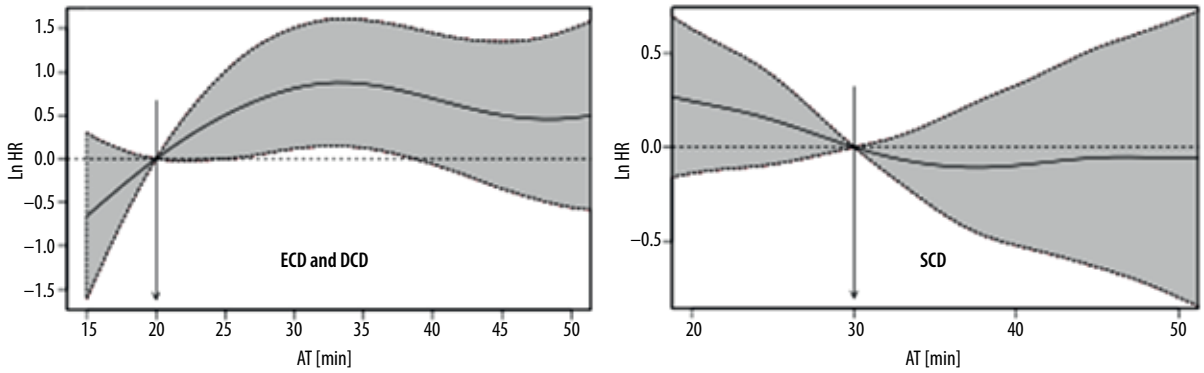

Figure 6. The AT-related risk of graft loss is specific for different donor organs. The graft-specific threshold for anastomosis times associated with reduced outcome was analyzed in a Cox regression with penalized splines. The non-linear correlation of AT and risk of graft loss is specific for ECD/DCD *vs.* SCD organs. In ECD/DCD organs, the risk of graft loss increases beyond an AT >20 min and peaks at 32 min, whereas prolongation of AT does not significantly influence SCD graft survival.

The detrimental synergism of DGF and donor age in Kaplan-Meier curves that we observed was confirmed by other studies [5,19]. Lapointe stated that death-censored graft survival is significantly impaired by DGF for donors >60 years old. In contrast, in donors <60 years old there was no significant increase in risk of graft loss [5]. A UNOS database analysis concluded that all donor age categories affect DGF, with the risk of DGF increasing with each year of increase in donor age [19]. In this study, CIT was a risk factor for DGF, as well as early and late allograft failure, but, interestingly, ECD donor status was not associated with DGF. This latter finding correlates with our multivariate analysis in elderly recipients (Table 3) and is presumably related to the fact that donor age *per se* may not pose a risk for DGF; rather, concomitant age-related factors such as ischemia times, donor-related co-morbidities (e.g., time on dialysis, history of hypertension or diabetes, and donor cause of death) and immunological factors may render older organs a risk factor for DGF.

The second major risk factor for DGF in elderly recipients was anastomosis time. In this context, the association of longer anastomosis times with DGF may be related to a more complex vascular status in this patient group, contributing to the correlation of AT and DGF in our study. Marzouk et al. reported that an AT >29 min was associated with a 3.8-fold higher risk of DGF [15]. However, there was no further discrimination between types of grafts. Similarly, a recent analysis from our department reported inferior patient and graft survival following AT>30 min [14]. Of note, 30-min AT represented the median AT in this study and was not stratified for age groups. It has been shown that warm ischemia causes more pronounced histological deterioration in older organs than in younger organs [11].

However, the literature on warm ischemia in kidney transplantation from living or brain-dead donors is scarce [20–22]. To the best of our knowledge, our study is the first to analyze cut-off values for anastomosis time in ECD/DCD organs. Thereby, prolonged AT in SCD organs had a negative impact on survival of younger patients. In this donor-recipient combination, younger and more immunogenic organs underwent prolonged ischemic injury and were then engrafted into immunocompetent hosts, thus being prone to a strong immunological reaction [17]. In contrast, the correlation of AT and graft survival was significantly different for ECD grafts. Since SCD grafts (with any AT) had a significantly better outcome than ECD/DCD grafts with the same AT, measures for a fast anastomosis in old kidneys may contribute to improving graft survival. In this context, it should be noted that ECD graft outcome also correlates with other factors such as donor and recipient related comorbidities, and a causal relationship between ischemia times and graft outcome has not been proven. However, this is not only about "the older, the faster". As the correlation of AT and risk of graft loss is not linear, there is a distinct reference time of 20 min, after which the risk of graft loss increases. Likewise, there is a cut-off time of 800 min for CIT, beyond which a non-linear increase in risk occurs. Thus, reports of an increasing risk of DGF with every minute of CIT are not depicting the true picture. Rather, there seems to be a threshold of ischemic injury beyond which an old organ cannot recover. This threshold is different for SCD and ECD organs and needs to be acknowledged. While the cut-off CIT in our study was in accordance with other published CIT associated with good graft function [2,9,10], the ECD threshold for AT was lower than expected and lower than reported in the literature [14,15]. This can be explained by the heterogeneous patient groups in those studies, comprised mostly of recipients of younger organs.

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Taken together, ECD graft outcome depends on a multitude of factors, among which ischemia times can be more easily decreased than other factors. Keeping CIT below 13.3 h and AT below 20 min may help to obtain graft survival comparable to that seen in SCD organs. Acknowledgement of these critical thresholds will support better outcomes of marginal grafts.

Conclusions

Our study was limited by the fact that it was retrospective and a single-center analysis in which ECD and DCD grafts have been summarized into one group of marginal donor grafts. In addition, subgroup analyses such as elderly recipients of SCD grafts may be impaired by the smaller group size. Recipient groups in our study were heterogeneous in that significant risk factors such as type of donor graft, immunological factors (HLA-Mismatch, retransplantation rates), and recipient CMV status differed significantly. Besides, AT in elderly recipients may in part reflect a more difficult surgical case, affecting DGF rates in this group. Moreover, data were collected in a time period of 10 years, thereby reflecting changes in immunosuppression and donor and recipient characteristics that may not have been recorded.

References:

1. Bahde R, Vowinkel T, Unser J: Prognostic factors for kidney allograft survival in the Eurotransplant Senior Program. Ann Transplant, 2014; 19: 201–9
2. Frei U, Noeldeke J, Machold-Fabrizii V et al: Prospective age-matching in elderly kidney transplant recipients – a 5-year analysis of the Eurotransplant Senior Program. Am J Transplant, 2008; 8: 50–57
3. Karatzas T, Bokos J, Katsargyris A et al: Advanced donor age alone is not a risk factor for graft survival in kidney transplantation. Transplant Proc, 2011; 43: 1537–43
4) Galeano C, Marcén R, Jimenez S et al: Utilization of elderly kidney donors (>70 years) does not affect graft survival in the medium term. Transplant Proc, 2010; 42: 3935–37
5. Lapointe I, Lachance JG, Noël R et al: Impact of donor age on long-term outcomes after delayed graft function: 10-year follow-up. Transplant Int, 2013; 26(2): 162–69
6. Melk A, Schmidt BM, Braun H et al: Effects of donor age and cell senescence on kidney allograft survival. Am J Transplant, 2009; 9(1): 114–23
7. de Fijter JW, Mallat MJ, Doxiadis II et al: Increased immunogenicity and cause of graft loss of old donor kidneys. J Am Soc Nephrol, 2001; 12: 1538–46
8. Slegtenhorst BR, Dor FJ, Elkhal A et al: Mechanisms and consequences of injury and repair in older organ transplants. Transplantation, 2014; 97(11): 1091–99
9. Boesmueller C, Biebl M, Scheidl S et al: Long-term outcome in kidney transplant recipients over 70 years in the Eurotransplant Senior Kidney Program: A single center experience. Transplantation, 2011; 92: 210–16
10. Fabrizii V, Kovarik J, Bodingbauer M et al: Long-term patient and graft survival in the Eurotransplant Senior Program: A single-center experience. Transplantation, 2005; 80: 582–89
11. Denecke C, Yuan X, Ge X et al: Synergistic effects of prolonged warm ischemia and donor age on the immune response following donation after cardiac death kidney transplantation. Surgery, 2013; 153(2): 249–61
12. Lee KW, Simpkins CE, Montgomery RA et al: Factors affecting graft survival after liver transplantation from donation after cardiac death donors. Transplantation, 2006; 82(12): 1683–88
13. Snoeijs MG, Schaefer S, Christiaans MH et al: Kidney transplantation using elderly non-heart-beating donors: A single-center experience. Am J Transplant, 2006; 6(5 Pt 1): 1066–71
14. Weissenbacher A, Oberhuber R, Cardini B et al: The faster the better: Anastomosis time influences patient survival after deceased donor kidney transplantation. Transpl Int, 2015; 28(5): 535–43
15. Marzouk K, Lawen J, Alwayn I, Kiberd BA: The impact of vascular anastomosis time on early kidney transplant outcomes. Transplant Res, 2013; 2(1): 8
16. Denecke C, Bedi DS, Ge X et al: Prolonged graft survival in older recipients: Impairment is determined by impaired effector T-cell but intact regulatory T-cell responses. PLoS One, 2010; 5(2): e9232
17. Tullius SG, Tran H, Guleria I et al: The combination of donor and recipient age is critical in determining host immunoresponsiveness and renal transplant outcome. Ann Surg, 2010; 252(4): 662–74
18. Smits JMA, Persijn GG, van Houwelingen HC et al: Evaluation of the Eurotransplant Senior Program. The Results of the first year. Am J Transplant, 2002; 2: 664–70
19. Moers C, Kornmann NSS, Leuvenink HGD, Ploeg RJ: The influence of deceased donor age and old-for-old allocation on kidney transplant outcome. Transplantation, 2009; 88: 542–52
20. Roodnat JI, Mulder PG, Van Riemsdijk IC et al: Ischemia times and donor serum creatinine in relation to renal graft failure. Transplantation, 2003, 75: 799–804
21. Irish WD, Ilsley JN, Schnitzler MA et al: A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant, 2010; 10: 2279–86
22. Hellegering J, Visser J, Kloke HJ et al: Deleterious influence of prolonged warm ischemia in living donor kidney transplantation. Transplant Proc, 2012; 44: 1222–26

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